CLINICAL ASPECTS OF NEPHRITIS*

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THE TERM nephritis embraces a number of morbid states with widely diversified etiological, pathological and clinical characteristics. An attempt to discuss the clinical aspects of various types of Bright's disease this evening would be futile. Likewise, a discussion of the symptomatology of one or more forms of nephritis could serve no constructive purpose. Consequently, I have elected to limit myself to the consideration of certain problems concerning that entity commonly known as glomerulonephritis.

All recent studies indicate that there is, as a rule, a close relationship between infection of the upper respiratory tract and the onset of acute glomerulonephritis. In recent and carefully controlled studies in which bacteriological and immunological observations have been made, the onset of acute glomerulonephritis has, in the vast majority of instances, been found to be associated with evidence of infection by the hemolytic streptococcus (Group A of Lancefield). Thus, Seegal and his coworkers found that the antistreptolysin titer of the blood was significantly increased in seventy-six of eighty consecutive patients suffering from acute glomerulonephritis, and in most of the cases it reached amazingly high levels. Longcope reported the presence of infection with the hemolytic streptococcus in 95 per cent of his patients.

In other instances, it now seems certain that acute glomerulonephritis develops secondary to infections due to agents other than the hemolytic streptococcus. A number of cases of acute nephritis have been reported following pneumococcal pneumonia. In most of these, secondary streptococcal infection has not been eliminated as a possible cause, but Seegal has recently followed two cases of postpneumonic nephritis in which there was no evidence of secondary streptoccal infection as determined by repeated antistreptolysin measurements. In bacterial endocarditis due

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to the streptoccus viridans also, glomerulonephritis not infrequently develops and is superimposed upon embolic nephritis without bacteriological or immunological evidence of invasion by the hemolytic streptococcus. It seems probable that in rare instances, acute glomerulonephritis may be initiated by still other organisms and that these need not necessarily gain entry to the body through the respiratory tract.

The role of infection in the etiology of *chronic* glomerulonephritis is far less clear than in the acute form of the disease, although exacerbations of chronic nephritis accompany or follow intercurrent infection with the streptococcus hemolyticus with striking regularity. In contrast with acute glomerulonephritis which usually develops ten to twenty days following an acute infection, chronic nephritis usually develops so insidiously that its onset is, as a rule, unrecognized. It seems certain that many cases of chronic nephritis begin as acute glomerular nephritis but the actual per cent is difficult to determine as it is often impossible to differentiate between the onset of acute nephritis and the exacerbation of an apparently quiescent chronic process. In Longcope's series about 40 per cent of the patients with acute nephritis developed active and progressive chronic nephritis. On the other hand, Lyttle, in studying children, in whom the outlook is admittedly favorable, has found that less than 5 per cent develop the chronic form of the disease.

In addition to the fact that chronic nephritis usually develops without definite relation to a preceding acute infection, there are also immunological differences between this and the acute form of the disease. Whereas the antistreptolysin titer of the blood may increase in chronic nephritis associated with streptococcal infection, it rarely reaches the high levels seen in acute nephritis. The significance of this difference in the immune response in the acute and chronic forms of the disease remains to be determined.

Mechanism of Glomerulonephritis.—While the relationship of hemolytic streptococcal infection to the onset of nephritis, at least in the acute form, is recognized, this knowledge has not as yet materially advanced our understanding of the mechanisms involved in the genesis of the disease. The fact that the onset of acute nephritis does not accompany but rather follows an acute infection offers evidence against the idea that the disease results from direct and immediate damage of the kidneys by bacteria or bacterial products. In 1912, Escherich and Schick expounded the idea that acute nephritis was not caused by acute infection but by

the immune reactions resulting from it. This concept may offer a satisfactory explanation for the latent period which elapses between the onset of infection and the onset of nephritis.

There have been many futile attempts to produce a disease in animals which shares the characteristics of glomerulonephritis in man. However, one line of approach, begun in 1900 by Lindemann and by Pierce in 1904 and elaborated by Masugi in 1929 and by Smadel and Farr since that time, has yielded interesting and important results. The general technique employed by these investigators is based upon the principle of the development of organ-specific antisera. If an emulsion of normal rat kidney is repeatedly injected into the peritoneum of a rabbit, a rabbit anti-rat kidney serum is produced. If one, two or three doses of this serum are injected intravenously into rats, acute nephritis develops. This disease may heal completely or it may go on to a chronic form associated with persistent and progressive albuminuria, cylindruria, edema, hypertension, anemia, nitrogen retention and a fatal decrease in renal function. The renal lesions bear a close resemblance to chronic glomerulonephritis in man.

The most significant feature of these studies is that they demonstrate the possibility of initiating chronic and progressive renal disease through the action of a single insult, in this case a dose of antikidney serum injected into a normal animal. Of added interest is the recent and important observation of Farr and Smadel that the course of the nephritis induced by the injection of nephrotoxic serum can be influenced by the amount of protein in the diet. If the diet of the rats contains only 5 per cent protein, the acute nephritis heals with great regularity in about three weeks. If, on the other hand, the diet contains 40 per cent protein, the disease progresses and the animals all die of chronic nephritis.

It is tempting to infer that a mechanism similar to that described in rats is responsible for glomerulonephritis in man. In order to extend the analogy, we must hypothecate that the hemolytic streptococcus or other bacteria produce somewhere in susceptible human beings nephrotoxic sera. These may give rise to acute nephritis which may or may not become chronic. It is possible that in man, as in the rat, another factor such as that of protein ingestion may serve to make progressive the disease initiated by a nephrotoxic serum. There is unfortunately, at the present time, no experimental evidence suggesting that nephrotoxic sera can be developed in response to the injection of bacterial products.

This speculative discussion has no practical application, but it indicates the trend of present day thought in relation to the possible mechanism involved in the production of glomerulonephritis. However, the observations on the deleterious effect of large amounts of protein in the diet are sufficiently striking to reopen the question of the place of protein in the diet in human nephritis.

The *diagnosis* of acute glomerulonephritis in its characteristic form offers but little difficulty. When, however, albumin, casts and red blood cells appear in the urine in small but definite quantities without extrarenal signs, either during or after an acute infection, the problem of diagnosis becomes difficult or even impossible. A number of students of nephritis circumvent these diagnostic dilemmas by applying the term focal nephritis to these doubtful cases, but in the writer's opinion the introduction of another term does not clarify the issue. If mild albuminuria, cylindruria and microscopic hematuria persist for more than one or two weeks, it seems probable that acute glomerulonephritis is present. If the changes disappear in a shorter time, it is best to admit that the diagnosis is uncertain. Minute decreases in renal function as measured by the urea clearance test may result from disorders other than nephritis and do not alone simplify the diagnostic problem. Frequently, often repeated urine examinations, a careful record of body weight which, in the absence of visible edema, may give evidence of water retention or diuresis and numerous blood pressure determinations may give transient but convincing evidence favoring the diagnosis of acute glomerulonephritis.

The difficulties besetting the physician in establishing a diagnosis of acute glomerulonephritis are emphasized by recent studies of urinary changes in acute rheumatic fever and in scarlet fever. In the former, in at least 15 per cent of the patients with the active form of the disease, red blood cells and small amounts of albumin appear in the urine at some time and yet only about 3 per cent prove to have associated acute glomerulonephritis at death. In scarlet fever, Lyttle, applying Addis' quantitative method for the determination of protein, casts and cells in the urine, found consistently a moderate transient increase above the accepted limits of normal. This occurred between eight and forty-five days after the onset of the attack of scarlet fever. Lyttle found similar changes in the urine after other infections due to the streptococcus hemolyticus, but did not find them with any regularity after infection with

other organisms. It seems unlikely that all patients suffering from scarlet fever and other streptococcal infections develop acute glomerulonephritis. Whether or not, however, the difference between this micronephritis or "renal irritation" and true acute glomerulonephritis is qualitative or quantitative cannot be settled at this time.

The *differentiation between acute glomerulonephritis and the chronic form of the disease* is of great importance because of the difference in prognosis and therapeutic indications. If urine examinations happen to have been made just prior to the onset of the attack, the problem is of course simple. Without knowledge of the medical background of the patient, it is often difficult and occasionally impossible to tell whether the patient's disease represents the beginning of acute nephritis or an acute exacerbation of chronic glomerulonephritis. If the latent period between acute infection and the appearance of renal disease is greater than ten days, it favors the diagnosis of acute nephritis because, in the chronic form of the disease, the flare-up usually occurs during the acute infection or shortly thereafter. When the signs of advanced and protracted renal disease are present, the diagnosis of chronic nephritis is justifiable. In the absence of these guides, diagnosis frequently has to be deferred until the subsequent course has been observed.

Patients with acute glomerulonephritis either recover completely or their disease progresses to the chronic form or they die during the acute attack. A fatal outcome occurs in less than 5 per cent of the cases. In children, complete recovery occurs in about 90 per cent of hospitalized patients but in adults the prognosis is definitely less favorable. However, it is difficult to determine the actual incidence of recovery because, as has been stated, an apparent acute nephritis may in reality represent an exacerbation of the chronic form of the disease, hitherto unrecognized. Furthermore, many patients with mild acute nephritis undoubtedly recover without ever coming to the attention of a physician and are consequently not included in statistical studies. Finally, in a number of mild cases, it is impossible to be certain that nephritis is present. Be that as it may, estimates of the frequency of recovery in adults vary from about 15 to 70 per cent.

It is impossible to predict the outcome of acute glomerulonephritis early in its course. However, in those instances in which the constitutional symptoms of the preceding infection have been severe, it appears to be particularly good. Furthermore, complete recovery occurs rapidly

in many patients even though they present alarming extrarenal manifestations early in the course of the disease, whereas chronic nephritis develops in others with an apparently benign form of the disease. When significant impairment of renal function persists for more than 3 or 4 months, the outlook for complete recovery is almost invariably bad.

The duration of the attack of acute glomerulonephritis varies enormously. In a number of cases, even when the diagnosis appears established beyond doubt, complete recovery may occur in the course of a few days. In other cases the disease may persist for more than a year and still terminate favorably. In these cases the extrarenal manifestations of edema, hypertension and nitrogen retention disappear, as a rule, in the course of a few weeks and the persistence of the disease process is demonstrable by the urinary changes alone.

According to Longcope and others, the duration of an attack of acute nephritis and the tendency to chronicity are definitely related to the persistence of infection by the hemolytic streptococcus. However, Seegal and his coworkers find that in a number of patients, the disease progresses in the absence of persistent or recurrent bacteriological or immunological evidence of infection. Furthermore, they have found that recovery may occur despite the persistence of definite infection.

Of great academic interest and also of great importance for the peace of mind of the patient is the fact that once completely recovered, i.e., after the disappearance of albumin, red cells and casts from the urine, there appears to be no danger of the development of chronic nephritis. Thus, E. N. Loeb, Seegal, Lyttle and Jost have shown in a series of eight patients, that following recovery from acute glomerulonephritis a second infection caused no return of nephritis. In these patients, the infection preceding the onset of the attack of acute nephritis and the second infection occurring after complete recovery were proven bacteriologically and by means of antistreptolysin determinations to be due to the streptococcus hemolyticus. In three other patients, transient hematuria or albuminuria or both developed with the second infection, but none of the eleven patients developed chronic glomerulonephritis.

I should like now to discuss a few points in relation to the diagnosis of chronic glomerulonephritis. The diagnosis is, as a rule, easily established on the basis of the continued presence of albuminuria, cylindruria and varying degrees of hematuria either with or without the extrarenal manifestations of the disease. At times, however, it presents a trying

problem and the difficulties in distinguishing the acute and chronic forms of the disease have been mentioned. The differentiation between chronic glomerulonephritis and arteriolar nephrosclerosis is sometimes impossible but is of little importance except for academic reasons.

The differentiation between the nephrotic phase of chronic glomerulonephritis and true nephrosis also offers difficulties and is of importance because in the latter complete recovery takes place in about 50 per cent of the cases. Both conditions have in common, massive albuminuria, edema, decrease in the serum protein content with a tendency toward inversion of the albumin-globulin ratio, lipemia and often lowering of the basal metabolic rate. The diagnosis of chronic nephritis becomes probable if, in addition to these signs, there be enlargement of the heart, marked hypertension, changes in the eyegrounds, significant impairment of renal function or numerous red blood cells in the urinary sediment. The age of the patient also has significance since true nephrosis rarely occurs in adults. The difficulties encountered in the diagnosis are exemplified by the following case record. A boy of fourteen developed headaches and edema about two weeks after a head cold. On examination, he had massive edema, and a blood pressure level which reached 160/100. His urine showed the presence of large amounts of albumin, many casts and occasional red cells. His blood urea rose to 100 mg. per 100 cc. This patient was believed to have chronic glomerulonephritis of the nephrotic type. He subsequently died from pneumococcus peritonitis and examination postmortem demonstrated the presence of pure lipoid or true nephrosis.

The differentiation between latent glomerulonephritis and orthostatic albuminuria presents difficulties in adolescents in whom no significant disturbance of renal function can be determined by the usual tests. The evidence favors an orthostatic process if the albuminuria disappears with bed rest but this is, however, not entirely conclusive, as the albuminuria in some cases of latent nephritis may diminish greatly with rest and increase with activity. If hypertension or other extrarenal manifestations are present, the problem of diagnosis is simple. In a number of cases, only prolonged observation with repeated urine examinations will serve to clarify the diagnosis.

It must be borne in mind that the picture of advanced renal insufficiency often results from kidney disease other than chronic nephritis. In those cases in which the history is in doubt, and in which pyuria plays

a prominent part, if bouts of fever have been present or if the clinical picture is in any way unusual, it is essential that x-ray examination and pyelography be employed.

Finally, it should be recognized that albuminuria, casts and red blood cells appear in the urine in cardiac decompensation, in jaundice and in severe febrile disease. Thus, in cardiac insufficiency, in addition to the urinary changes described, the blood urea may reach 0.70 gm. per l. or more, the blood urea clearance may be diminished and the phthalein excretion often falls to 30 per cent or even less. Hence, it is often impossible to state whether chronic nephritis is or is not present and decision must be postponed in such patients until cardiac compensation is re-established. If eyeground changes, fixation of the specific gravity of the urine, and marked hypertension accompany cardiac failure, it is probable that nephritis is also present.

While the *prognosis* in patients with chronic glomerulonephritis is ultimately bad, the velocity with which the disease reaches its fatal termination is extremely variable. Except in the terminal stages, it is practically impossible to predict the probable life span of a patient on the basis of clinical observations and laboratory studies, made at any one time. Repeated observations and studies of renal function made over a period of months or years are of far greater value insofar as they may reveal an approximate curve of the velocity of progression of the disease. Despite the most careful supervision, however, prediction of the course of chronic glomerulonephritis is hazardous. For example, a patient may be observed during an acute exacerbation of the disease. After some months, activity may subside and the patient may lead a normal and useful existence for many years before uremia develops. Thus, in a patient seen at the Presbyterian Hospital with massive edema, hypertension, nitrogen retention, albuminuria and hematuria, the blood pressure now, twenty years later, is normal and only albuminuria and cylindruria without impairment of renal function persist. In other cases of apparently the same initial severity, the disease may progress to a fatal termination in a few months.

There are certain criteria, which although not infallible, have real prognostic value. When the disease is associated with rapidly progressing hypertension, when severe anemia develops abruptly, when in the course of a few months the power of concentration is lost and when activity of the disease as manifested by copious microscopic hematuria persists

over a period of three to four months, the duration of life is usually less than two years. Furthermore, if decompensated renal function appears and the blood urea rises progressively to levels of perhaps 1 gram per l. the prognosis is equally grave. The presence of papilledema, combined with hemorrhages and patches of exudate in the eyegrounds also usually indicates that the duration of life will be less than two years. The same outlook may be anticipated when the urea clearance falls below 10 per cent of normal or when the phthalein excretion fails completely.

In order to temper the significance of these dogmatic statements, I should like to mention briefly the record of one patient who broke all the accepted rules. In this girl, after six years of active glomerulonephritis, the excretion of phthalein in two hours was nil, her blood urea was 90 mg. per 100 cc. and her creatinine was 6 mg. per 100 cc. Despite this, the patient worked most of the time during the following six years and annual observations showed not only the persistence of markedly impaired renal function but further accumulation of urea in the blood. The patient finally died in uremia and the diagnosis was confirmed at autopsy. Cases of this kind occur with sufficient frequency to warrant extreme caution in offering a bad prognosis for the probable duration of life.

Before concluding, I should like to comment briefly on the *treatment* of chronic nephritis. It must be recognized that, in the treatment of chronic glomerulonephritis, we are dealing with the problem of therapy in a disease which is incurable at the present time. Hence, the physical comfort of the patient and, still more important, his peace of mind, deserve first consideration. If this principle be kept in mind, the patient may be spared the distress and discomfort associated with measures such as unnecessary dietary restriction, excessive purging, sweating and colonic therapy which are not only futile but which may be actually harmful. This apparent therapeutic nihilism, I believe, in reality better serves to make the patient's existence tolerable than does over-energetic treatment. This point of view does not imply that a purely laissez faire attitude should be adopted. On the contrary, every effort should be made to introduce those measures which may retard the progress of the disease and it is essential that the patient be forewarned against those factors which appear to accelerate it.

In the *dietetic treatment* of chronic nephritis only questions of protein, salt and fluid deserve consideration. It is our impression that the

importance of *protein* restriction in some cases and of forced protein feeding in others has been over-emphasized in recent years. In chronic nephritis, characterized by albuminuria, cylindruria and some hematuria without edema or advanced renal insufficiency, there appears to be no reason for regulating the amount of protein in the diet beyond suggesting that the patient follow the adage of "moderation in all things." In the presence of nitrogen retention, the amount of protein should be restricted because large amounts undoubtedly contribute to the retention of nitrogenous products. In these patients, the amount of protein may perhaps ideally be reduced to 40 or 50 grams a day. If, however, anorexia results in loss of weight and strength, it is far better to allow the patient to choose his foodstuffs without regard to theoretical consideration than to have him burn his own body protein and increase his non-protein nitrogen retention from that source.

When Epstein pointed out the importance of hypoproteinemia in the genesis of nephrotic edema twenty years ago, he logically introduced high protein feeding to compensate for protein lost in the urine. We all employ this diet today in the treatment of the edematous chronic nephritic, but I think it is fair to say that we are almost always disappointed in its effect upon the level of the serum proteins and amount of edema present. Nevertheless, it seems rational to attempt to maintain nitrogen balance in these patients in order to prevent the further depletion of serum albumin. This can usually be accomplished by the ingestion of about 100 to 120 grams of protein a day. I sincerely doubt that diets much higher in their protein content accomplish more and, in addition, they are distasteful to the patient deprived of salt.

Our feeling concerning the place of salt restriction can be expressed in a few words. Sodium salts are essential for the formation of edema fluid. Hence, in the presence of abnormal fluid retention, regardless of the reason for its appearance, rigid limitation of sodium must be enforced. It is our opinion that there is no other sound basis for salt restriction in the treatment of nephritis and that employment of this therapeutic measure in the absence of edema often accentuates anorexia, nausea and vomiting.

In patients with chronic nephritis, consideration of *fluid* ingestion is important only under two conditions. First, in the presence of edema, the intake of water should be restricted in accordance with the degree of retention, the acuteness of the symptoms and the presence of cardiac

insufficiency. Second, with the advance of renal insufficiency, the fluid intake should be increased to compensate for the loss of the power of concentration. If, however, the intake of fluid exceeds that amount which can be eliminated by the renal units still capable of function, edema will appear.

The use of diuretics is contraindicated in patients with chronic nephritis exhibiting either hematuria, gross or microscopic, or significant impairment of renal function.

The importance of the close relationship between recurrent or persistent infection of the upper respiratory tract and exacerbations of chronic nephritis can not be over-emphasized. Both the physician and the patient must look upon even a mild cold as a matter of concern and should treat the disorder accordingly. Tonsillectomy, in my opinion, should be performed routinely in patients with early nephritis and sinusitis merits rigorous attack. When, however, glomerulonephritis has progressed to the stage of advanced renal insufficiency, operative treatment of disease of the nose and throat has no place.

In conclusion, I should like to say that this brief sketch of certain aspects of glomerulonephritis in no way does justice to the scope of the title and I must add that I have considered only a few phases of the disease which seem to have particular interest at the present time.